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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/788,649 | 02/27/2004 | Thomas D. Madden | 480208.408D1 | 7233 |

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| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1615 | |

DATE MAILED: 06/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/788,649 | MADDEN ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S. Kishore, Ph.D | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *7-13,17,18 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-13,17,18 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment dated 3-18-05 is acknowledged. Claims included in the prosecution are 7-13, 17-18, and 21-29.

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young cited above.

The teachings of Young have been discussed above. What are lacking in Young are the teachings of claimed neoplastic agents.

However, since according to Young the empty liposomes influence the rate of release of the active agent, it would have been obvious to one of ordinary skill in the art with a reasonable expectation of success that any active agent release could be influenced by the empty liposomes irrespective of its nature. Young does not disclose the lipid: drug ratios; however, these are deemed to be obvious parameters manipulated by an artisan to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Young fails to teach that the release rate of intravenously administered liposomal composition can be influenced by including empty liposomes and that camptothecins and vinca alkaloids are known in the art to be administered intravenously. This argument is not found to be persuasive since the rejected claims are composition claims and not method of intravenously administering the composition. The examiner disagrees with applicant's statement that vinca alkaloids and camptothecins are known in the art to be administered intravenously and cites several references at the end of the office action which show the knowledge in the art of administration of these compounds by several modes including SC and IM injections.

3. Claims 7-13 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 91/04019 cited above.

WO discloses liposomes containing an active agent entrapped within and empty liposomes. The ratio of liposomes containing the active agent to the empty liposomes is 1:1 to 1:10,000. The active agents taught by WO include interferons and chemotactic peptides. The liposomal lipids taught include sphingomyelin and cholesterol. The ratios of the active agent to lipid fall within the claimed amounts. According to WO, the addition of empty liposomes increases the bioavailability of the therapeutic agent (abstract, page 6, line 17 through page 7, line 33, page 8, line 4 through page 9, line 17 and claims, in particular, claims 8, 21, 22, 27, 31 and 33). What are lacking in WO are the teachings of claimed neoplastic agents.

However, since according to WO the empty liposomes increase the bioavailability of the active agent, it would have been obvious to one of ordinary skill in the art with a reasonable expectation of success that any active agent's bioavailability will be increased by the empty liposomes irrespective of its nature. WO does not provide any specific examples of liposomes containing sphingomyelin and the ratios of the bilayer-forming lipid to cholesterol also appear to differ from instant ratios. However, it is deemed obvious to one of ordinary skill in the art to use sphingomyelin suggested by WO and vary the ratios of this bilayer-forming lipid to cholesterol to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that while the constraint on the route of administration is not immediately obvious from the specification, upon careful review of the entirety of WO 91/04019, the skilled artisan would understand that its teachings are limited to SC and IM administration. Applicant points out to summary section and pages 4-5 of the reference. The examiner disagrees and points out to page 10, line 16 et seq., where the reference teaches that any of the normal administration procedures may be used to introduce the encapsulated peptide or protein into the patient. This clearly implies modes of administration other than SC and IM routes. Furthermore, the reference teaches in Example 7, direct incubation of the liposomes and empty liposomes with serum, which is suggestive of modes of administration other than SC and IM and suggestive of IV mode of administration.

4. Claims 7-13, 17-18, and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) of record in combination with either Young or WO 91/04019 cited above.

Kirpotin discloses liposomal compositions wherein the active agent is in the precipitated form. The active agent according to Kirpotin can be any compound with ionizable groups. The active agents suggested by Kirpotin are antineoplastic agents, doxorubicin, vincristin, vinblastine and others. The liposomes are made of various phospholipids including sphingomyelin; the liposomes contain cholesterol. The lipid drug ratios in Kirpotin also appear to fall within the claimed ratios (abstract; col. 4, line 54 through col. 6, line 18; col. 9, lines 22-67; examples and claims). What are lacking in Kirpotin are the teachings of the inclusion of empty liposomes.

Young as pointed out above, discloses liposomes containing an active agent entrapped within and empty liposomes. The ratios of liposomes containing the active agent to empty liposomes are 0.1-1 to 10-200. The active agents taught by Young are anti-tumor agents such as doxorubicin. According to Young, the administration of such a mixture selectively controls the rate of release of the liposome entrapped active agent (abstract, col. 4, line 40 through col. 6, line 23, col. 10, lines 35-49, col. 15, lines 10-34, Example VIII and claims).

WO as pointed out above, discloses liposomes containing an active agent entrapped within and empty liposomes. The ratio of liposomes containing the active agent to the empty liposomes is 1:1 to 1:10,000. The active agents taught by WO

include interferons and chemotactic peptides. The liposomal lipids taught include sphingomyelin and cholesterol. The ratios of the active agent to lipid fall within the claimed amounts. According to WO, the addition of empty liposomes increases the bioavailability of the therapeutic agent (abstract, page 6, line 17 through page 7, line 33, page 8, line 4 through page 9, line 17 and claims, in particular, claims 8, 21, 22, 27, 31 and 33).

The inclusion of empty liposomes in the liposome compositions of Kirpotin would have been obvious to one of ordinary skill in the since such an inclusion would selectively controls the rate of release of the liposome entrapped active agent as taught by Young or empty liposomes increase the bioavailability of the therapeutic agent as taught by WO.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Kirpotin compared to Young and WO 91 is directed to an entirely different area of technology and that Kirpotin describes an approach for achieving a high concentration of liposome-encapsulated drug, which involves encapsulation of drug in a precipitated form. According to Applicant, in stark contrast Young and WO 91 are generally directed to methods of controlling release rates or increasing bioavailability of SC or IM-administered liposome-encapsulated drugs by including empty liposomes. The rationale behind this argument is not readily apparent to the examiner since irrespective of the nature of the encapsulated material, the liposomes taught by Kirpotin are still the liposomes and the advantages of using empty liposomes taught by Young and WO 91 would be the same irrespective of the nature of

the active material encapsulated within the liposomes and applicant has not shown that to be otherwise. In fact, applicant himself is claiming the active agent in both precipitated form and as free active agent in claim 17. Furthermore, according to applicant's own statement, Kirpotin teaches an alternate approach for achieving ***high concentration of liposome-encapsulated drug***, one of ordinary skill in the art would be motivated to use Kirpotin's liposomes since they have ***high concentration of encapsulated drug.***

5. Claims 7-13, 17-18, and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 of record in combination with either Young or WO 91/04019 cited above.

WO 99 discloses liposomal formulations containing various camptothecins in a precipitated form. According to WO, any phospholipid capable of forming liposomes can be used in preparing liposomes. The liposomes also contain cholesterol. The drug-lipid ratios taught by WO appear to fall within the claimed ratios (abstract, page 8, lines 8 through page 11, line 15; page 12, lines 1-7, Examples 3 and 4 and claims). What are lacking in WO are the teachings of the use of empty liposomes and the use of vinca alkaloids as the anti-tumor agents.

The teachings of Young and WO 91 have been discussed above.

The inclusion of empty liposomes in the liposome compositions of WO 99 would have been obvious to one of ordinary skill in the since such an inclusion would selectively controls the rate of release of the liposome entrapped active agent as taught by Young or empty liposomes increase the bioavailability of the therapeutic agent as

taught by WO 91. The use of vinca alkaloids instead of camptothecins with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since both Young and WO 91 teach the applicability of the method to any active agent.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the teachings of WO 99 are limited to camptothecins which are known in the art to be administered intravenously and therefore the skilled artisan would have no motivation to modify the teachings of WO 99 by adding empty liposomes to the liposomal camptothecins of WO 99 on the basis of either Young or WO 91 since their teachings regarding empty liposomes is clearly limited to SC and IM administered liposomal drug formulations. This argument is not found to be persuasive since WO 99 does not disclose intravenous delivery as the ***only means of delivery.*** On page 15, lines 13-19 WO 99 teaches that the route of delivery of liposome can also affect their distribution in the body and various routes of administration are envisioned. These statements imply the inclusion of the SC and IM administrations of Young or WO 91.

The following are cited of interest. 6,855,331 (col. 7, lines 15-47), 6,825,206 (col. 11, lines 42-50), 6,723,338 (col. 8, lines 3-12, col. 14, lines 45-49), 6664,223 (col. 2, lines 27-34), 6,627,614 (col. 2, lines 21-27 and col. 9, lines15-25) and 6,352,996 (col. 2, lines 22-27).

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK